Case Report

Metastatic Malignant Phaeochromocytoma: A Rare Entity that Underlies a Therapeutic Quandary

Wei-Hwang Wan, Kok-Yang Tan, Chin Ng, Khoon-Hean Tay, Kent Mancer,[1] Miah-Hiang Tay,[2] Whay-Kuang John Chia,[2] Khee-Chee Soo[3] and London Lucien Ooi,[3] Departments of General Surgery and [1]Pathology, Changi General Hospital, and Departments of [2]Medical Oncology and [3]Surgical Oncology, National Cancer Centre, Singapore.

Phaeochromocytoma is a rare condition that provides a diagnostic challenge as a result of its variable presentation. Treatment of metastatic malignant phaeochromocytoma is also not well defined owing to its rarity. We present four such cases and a review of the literature. The database of the Singapore Cancer Registry was used to trace all cases of metastatic malignant phaeochromocytoma from 1984 to 2004, and the case records were then reviewed retrospectively. There were four patients with metastatic malignant phaeochromocytoma seen in Singapore in the last 20 years. Their variable clinical courses were reviewed and compared with current knowledge and overseas experience in the literature. We further discuss the difficulties in diagnosis, and the dilemma in appropriate management of such cases. Phaeochromocytoma remains a commonly missed diagnosis unless a high index of suspicion is maintained. Malignant phaeochromocytoma has a variable clinical course. There is a place for radical surgery if this can render the patient free of gross disease, or when it can achieve symptom control for palliation and improvement in quality of life. In the metastatic context, debulking surgery does not appear to be of curative benefit, although it may be undertaken for good palliation. [*Asian J Surg* 2006;29(4):294–302]

Key Words: metastasis, phaeochromocytoma

Introduction

Phaeochromocytomas are rare tumours, occurring in less than five per million of the general population,[1] and affecting less than 1% of the hypertensive population.[2] Malignant forms of the condition are even rarer, forming 10–25% of all phaeochromocytomas, with a 5-year survival rate of 44% reported.[3]

Phaeochromocytoma is a medically challenging condition as it is potentially lethal if untreated and associated with very high morbidity if unsuspected, yet it can be relatively easily determined and localized if the diagnosis is made correctly. The management of malignant forms of the condition that manifest with local invasion or distant metastases is less straightforward given its rarity and remains controversial at the present time.

We present a case series of four patients with metastatic malignant phaeochromocytoma and illustrate their highly variable clinical courses and outcomes. We go on to compare our Singaporean experience against the current literature with respect to difficulties in arriving at the diagnosis as well as the role of surgery and other adjunctive treatment modalities in the optimal management of such patients.

Address correspondence and reprint requests to Dr Wei-Hwang Wan, 7C Lloyd Road, Singapore 239094.
E-mail: wanweihwang@yahoo.com.sg • Date of acceptance: 10 March 2006

Patients and methods

All cases of metastatic malignant phaeochromocytoma in Singapore in the last 20 years from 1984 to 2004 were identified through a search of the database maintained by the Singapore Cancer Registry. Their medical records were reviewed with particular attention paid to intervention at a given stage and the disease outcome. Four cases were identified. They are presented below and summarized in the Table.

Table. Summary of case series

Patient	1	2	3	4
Age (yr)/sex	40/M	41/M	46/F	56/F
Presentation	Acute right hypochondrial pain mimicking acute abdomen	Nonfunctional large right-sided abdominal mass	Solitary right functional adrenal tumour	Solitary left functional adrenal tumour
Tumour size (cm)	16.5 × 14.5 × 11.5	16 × 12 × 12	10 × 6 × 6	7 × 5 × 5
Locally invasive	Yes, to right lobe of liver	Yes, to retrohepatic IVC and RA	No invasion past capsule	No
Metastatic	Yes, widespread, to the lungs, liver and bone	Yes, two solitary pulmonary nodules	Yes, to pleura and paratracheal nodes in right side of chest only	Yes, tumour recurrence detected in contralateral adrenal 6 years later, and liver and lung metastases 1 year later
Surgery	Right hemihepatectomy and tumour debulking	Two-staged main tumour resection via laparotomy followed by tumour thrombus excision via median sternotomy	Initial right adrenalectomy, subsequent right thoracotomy and resection of metastatic nodules	Left adrenalectomy repeated for the right side, no surgery for metastases
Outcome of surgery	Pain and symptom palliation	Stormy postoperative course in ICU with ARF after first operation, died from MODS after second operation	Small amount of residual tumour	NA
Chemotherapy	Given three courses, one of CVD and two of paclitaxel	Planned but not started, patient died 4 days after second surgery	Patient declined	Initial 11 cycles of CVD and five cycles of paclitaxel with partial response, further chemotherapy with anzatax, navelbine, gemcitabine and doxorubicine with no response
Disease progression	Yes, increase in size of metastases and pleural effusion	NA	No	Yes, recurrence of metastases and rise in biochemical markers
Outcome	Died from disease progression 1 year after initial presentation	Died from MODS 4 days after surgery	Alive 2 years after resection of metastases and 5 years after initial diagnosis	Alive 3 years after starting chemotherapy despite disease progression and unresponsive to chemotherapy now

IVC = inferior vena cava; RA = right atrium; ICU = intensive care unit; ARF = acute renal failure; MODS = multiorgan dysfunction syndrome; NA = not available; CVD = cyclophosphamide, vincristine and dacarbazine.

Results

Demographics

The four patients were generally young and in their forties, with the oldest aged 56. There was an equal number of men and women, of which two men were Malay and two women were Chinese.

Mode of presentation

The mode of presentation was highly variable. Patient 1 presented with severe right hypochondrial pain associated with fever and diaphoresis, mimicking an acute abdomen. Computed tomography (CT) subsequently revealed a large 16.5 × 14.5 × 11.5 cm retroperitoneal tumour arising from the right adrenal (Figure 1A). Subsequent biochemical data confirmed the functional nature of the tumour giving rise to some of the symptoms, namely elevated 24-hour urine vanillylmandelic acid (VMA) of 210 μmol/day (0–34.3) and markedly elevated levels of 24-hour urinary catecholamines: epinephrine 2,857 nmol/day (0–1,709), norepinephrine 2,190 nmol/day (89–473) and dopamine 10,495 nmol/day (424–2,612).

Patient 2 presented with a large right-sided abdominal mass. He was otherwise asymptomatic. The 24-hour urinary VMA was within the normal range at 27.3 μmol/day, while the values for urinary normetanephrines and norepinephrine were only mildly elevated at 2,803 nmol/day (600–1,900) and 620 nmol/day (89–473), respectively.

Two patients presented with catecholamine excess after resection of the primary phaeochromocytoma.

Patient 3, a 46-year-old woman, presented with symptoms of catecholamine excess 4 years after the initial surgery. Her 24-hour urinary VMA was at the high-normal range at 1,664 μmol/day, but the urinary normetanephrines were definitely raised at 12,328 nmol/day. What was thought to be a local recurrence eventually proved to be metastatic

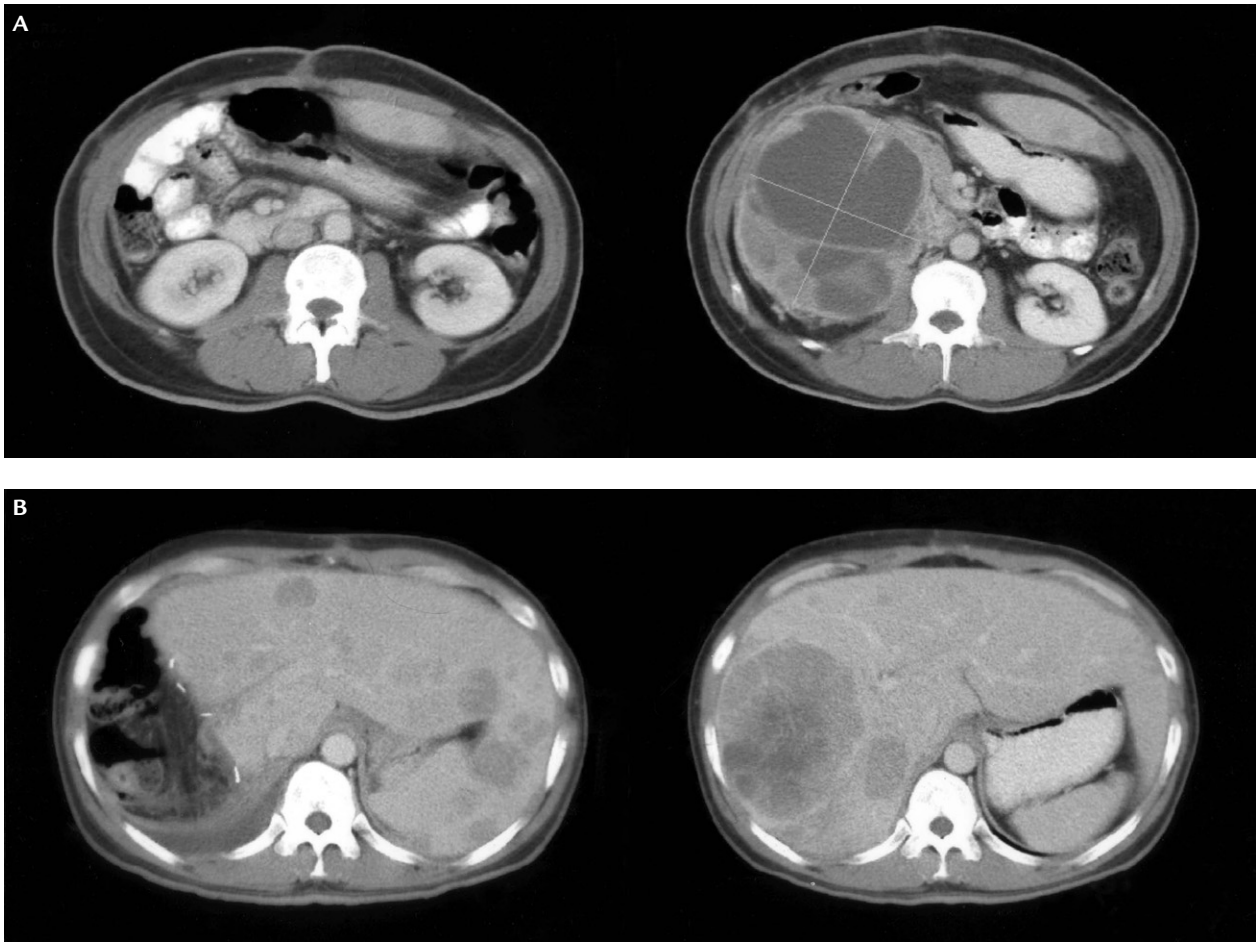

Figure 1. (A) Computed tomography (CT) on the left shows post eventual debulking surgery performed for the large primary retroperitoneal tumour that is shown at its largest diameter on the right. (B) Left: CT 1 month after right hemihepatectomy with bilateral lobe liver metastases. Right: CT shows the largest liver metastasis before resection.

lesions in the right pleura and paratracheal nodes. This was confirmed with meta-iodobenzylguanidine (MIBG) scans.

Patient 4, a 56-year-old woman, had a recurrence of symptoms of catecholamine excess attributed to phaeochromocytoma in the right adrenal 6 years after initial resection of left phaeochromocytoma in 1995. Metastatic lesions in the liver and lungs were detected on MIBG scans 1 year after the second adrenalectomy when a second repeat episode of her symptoms surfaced. She was admitted with flash pulmonary oedema secondary to catecholamine surge, which required her to be intubated and ventilated in the ICU. Her 24-hour urinary normetanephrine was found to be elevated at 7,700 μmol/day.

Tumour characteristics

The male patients had distinctly larger tumours of a size that was clinically palpable. Patient 1 had metastatic nodules in both lobes of the liver and lungs, as well as widespread metastases to the ribs, lumbar vertebrae and pelvic bone (Figure 1B). Patient 2 had locally invasive tumour to the retrohepatic inferior vena cava (IVC) and right atrium (RA) in addition to two small solitary pulmonary nodules.

Patients 3 and 4 had smaller but more biochemically active tumours. Findings at initial presentation did not demonstrate any capsular invasion. However, both patients were later found to have lesions in other remote sites of the body.

Operative procedures

Patient 1 was a case of unsuspected phaeochromocytoma at initial surgery. An emergency exploratory laparotomy was performed on the night of his admission as his presentation suggested a perforated gangrenous gallbladder empyema. However, a large retroperitoneal tumour with seeding of both lobes of the liver was found and no attempt at trial dissection was made. He subsequently underwent elective palliative debulking surgery about 1 month later. Prazosin 1 mg tds and propranolol 20 mg bd were used for preoperative α- and β-blockade. Surgery was necessitated as the patient developed pain and distension of the abdomen from the enlarging tumour and secondary to ascites. This limited his mobility and adversely affected his quality of life. For lack of sufficient information in the literature, it was also the consensus between the surgeon and oncologist that debulking surgery may offer the patient a less complicated chemotherapy course and a better chance at prolonging survival. Debulking of the primary right adrenal tumour with right hemihepatectomy was performed (Figures 2 and 3). Intraoperatively, the blood pressure surged to 220/120 mmHg when the tumour was manipulated, requiring intravenous glyceryl trinitrate, phentolamine, esmolol and labetalol for control. Postoperatively, there was no problem with blood pressure control and his recovery was uneventful. Histology confirmed metastatic phaeochromocytoma (Figure 4A–D).

Patient 2, after extensive discussion with the patient following the diagnosis of metastatic phaeochromocytoma, underwent radical surgery combined with postoperative chemotherapy in view of his young age. This was planned as a two-staged procedure to be performed at the same sitting, beginning with primary tumour resection via a midline laparotomy followed by excision of IVC and RA tumour thrombus via a median sternotomy. However, difficulties encountered during the first stage resulted in

Figure 2. Operative picture of the right adrenal tumour.

Figure 3. Operative picture of the right liver metastases.

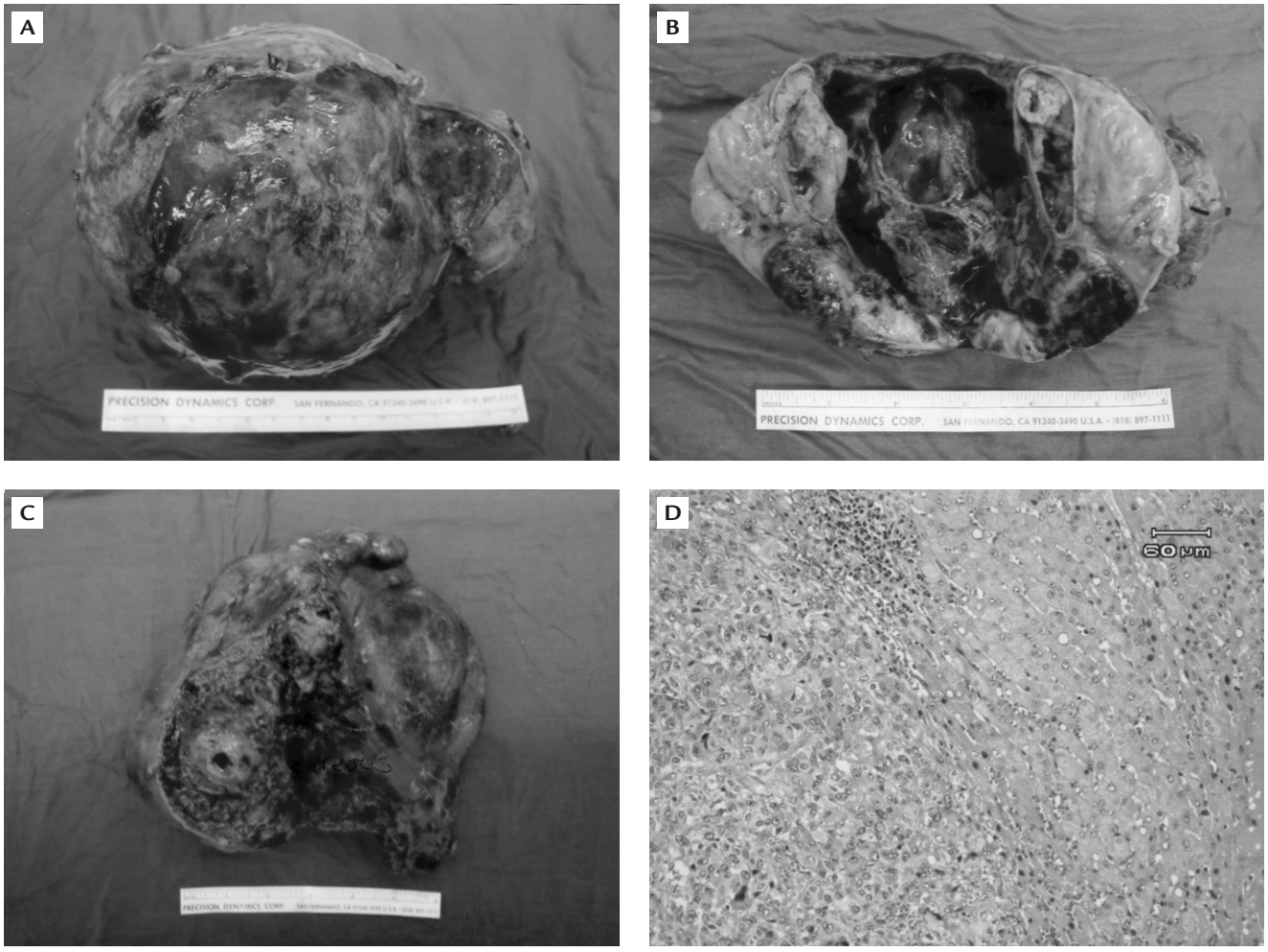

Figure 4. (A, B) Gross specimens of the adrenal tumour. (C) Gross specimen of the resected right lobe of the liver. (D) Microscopy of the liver metastases shows phaeochromocytoma.

a prolonged surgery time and haemodynamic instability. The decision was made to abandon the second stage and to perform the resection at a later date. The patient underwent a stormy postoperative course in the ICU complicated by coagulopathy and acute renal failure. The second stage was eventually performed 1 month after the first. A right atriotomy extending down to the IVC was required to remove the tumour together with a part of the anterior wall of the suprahepatic IVC. Unfortunately, he died 4 days after the second stage from systemic vasodilatory shock complicated by acute renal failure and acute respiratory distress syndrome.

Patient 3 had metastatic lesions isolated in the right lung pleura and paratracheal nodes 4 years after initial resection for functional right phaeochromocytoma. Surgery was intended to achieve near complete resection of tumour tissue and, hence, eradicate all the sequelae of functional catecholamine-secreting tumour, with a view to adjuvant chemotherapy postoperatively. This took place in the form of a right thoracotomy, resection of paratracheal mass and parietal pleural nodules, and segmental resection of the 10th rib together with pleural metastases.

Patient 4 had symptomatic phaeochromocytoma, which was found in her right adrenal gland 6 years after she had a similar disease presentation in her left adrenal. She had undergone adrenalectomy at each sitting with resolution of her symptoms. Recurrence of her symptoms of catecholamine excess 1 year later led to the discovery of lung and liver metastatic deposits. Surgery was no longer feasible and she agreed to go ahead with a chemotherapy regimen.

Chemotherapy

A baseline CT done 1 month after the debulking surgery for patient 1 already showed interval increase in the size of the lung, contralateral liver and bone metastases (Figure 5). He was started on a combination regimen of

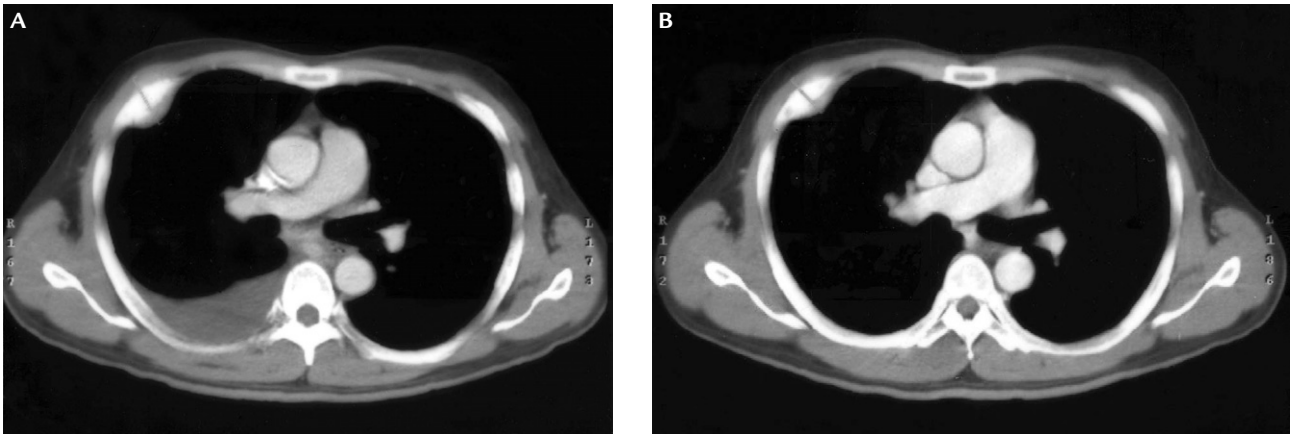

Figure 5. Computed tomography (CT) shows (A) development of right pleural effusion and increase in size of rib metastases compared to (B) CT 6 weeks prior, evident of progressive disease.

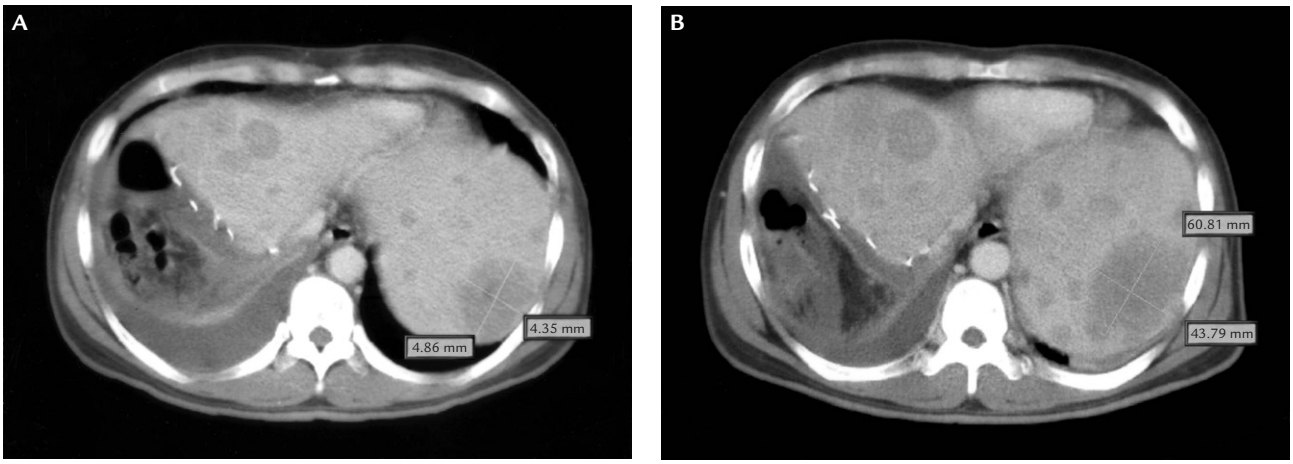

Figure 6. Computed tomography shows progressive disease with increase in size of liver metastases within a month despite debulking surgery and chemotherapy.

cyclophosphamide, vincristine and dacarbazine (CVD). This was converted to paclitaxel after a month when disease progression was noted on reimaging (Figure 6), based on previous anecdotal positive experience with the drug.

Patient 2 succumbed to the disease soon after surgery, and patient 3 declined chemotherapy for the small amount of residual tumour that remained after resection.

Patient 4 initially demonstrated good radiological and biochemical response to chemotherapy with dramatic tumour shrinkage in the metastatic sites. She received 11 cycles of chemotherapy with CVD over 1 year. Repeat CT scan showed resolution of multiple lung nodules and segment 4 liver metastasis. Her 24-hour urine normetanephrine also declined from 7,700 to 3,000 nmol/day. Her symptoms such as flushing also improved. This was continued with a further five cycles of paclitaxel chemotherapy. Repeat CT scans showed no relapse and the 24-hour urine normetanephrines also decreased to 1,800 nmol/day. For 2 years from the start of chemotherapy, the disease remained stable. However, disease progression was soon noted after that with a rise in 24-hour urinary normetanephrine, recurrence of lung and liver metastases and relapse of symptoms. She was administered further separate cycles of chemotherapy with anzatax, navelbine, gemcitabine and doxorubicin, but with no halt in disease progression.

Outcome of intervention

Patient 1 had significant symptomatic relief from pain and abdominal distension after debulking surgery for half a year. There was, however, disease progression, with CT evidence of interval increase in the size of the lung, contralateral liver and bone metastases. There was no response to two different courses of chemotherapy regimens.

Patient 2 succumbed from multiorgan dysfunction syndrome after making a difficult recovery from surgery.

Patient 3 benefited from both biochemical and tumour remission after an aggressive surgical approach to clear an apparently unilateral spread of metastases. Not only did subsequent serial CT scans show stable disease in the small residual right lung metastases, but she also remained symptom-free and averted the need for anticatecholamine drugs. She is well and enjoys a good quality of life.

Patient 4 had initial chemosensitive disease with the spread of the disease controlled with chemotherapy after complete excision of localized disease in each adrenal at two separate sittings. Unfortunately, she suffered from a relapse 2 years later and further chemotherapy was unable to halt disease progression.

Discussion

The clinical presentation of phaeochromocytoma can be varied. Hypertension, palpitations, headaches, sweating, weakness, lethargy, pallor, anxiety and depression have all been reported as presenting symptoms.[4,5] The nonspecific symptoms make phaeochromocytoma an underdiagnosed condition. It is estimated that it is diagnosed during life in less than half of the patients in whom it is found at autopsy.[6] Undiagnosed tumour formed 17% of cases in an 18-year review in Hong Kong,[7] and up to 75% in a series from the Mayo clinic spanning more than 50 years.[8] Thirteen of 17 deaths could be attributed at autopsy to the tumour or its catecholamine effect in another study looking at 46 cases over a 14-year period.[9] The description of patient 1 illustrates a case of unsuspected phaeochromocytoma where the predominance of abdominal signs was suggestive of peritonitis.

The diagnosis of malignancy is not clear-cut in phaeochromocytoma. The occurrence of phaeochromocytoma in sites normally devoid of chromaffin tissue, direct tumour invasion and overt metastases is usually definitive for malignant disease. However, on a cellular level, the usual histological criteria of malignancy like capsular invasion and mitotic figures are only poorly predictive of eventual biological behaviour. As such, some large tumours with poor histological prognostic features remain disease-free years after the primary resection, while belated metastatic spread and recurrent disease in the form of widespread metastases are well recognized in apparently benign tumours at primary resection. This is illustrated in the cases of patients 3 and 4.

Survival data in malignant phaeochromocytoma have shown two subsets of patients. In the first subset, which is approximately half of the patients, there is an aggressive course and most die within 4–5 years. In the other half, the course is more indolent and many survive for years without any targeted treatment.[10] There have been sporadic reports of prolonged survival even in patients with widely metastatic phaeochromocytoma.[11–13] Brennan and Keiser[14] reported three cases of unresectable metastatic disease with prolonged survival of 10–23 years with antihormonal agents and without any form of chemotherapy. Surgery, when performed at various points in their clinical courses, was to control local complications of metastatic disease and came in the form of cervical laminectomy, colostomy, femoral fracture stabilization, biliary bypass and adhesiolysis.

Musholt[15] in his review paper cites the uniformly poor prognosis of patients with tumours left *in situ* as sufficient justification for surgery as the treatment of choice even for tumour debulking only. There is, however, no data to show improved survival rates after tumour debulking to substantiate this approach. In general, surgery, if undertaken in metastatic cases, should be aimed primarily at resolving the complications of tissue destruction or obstruction by tumour masses. It is also indicated in tumour debulking with palliative intent in cases of massive tumours causing visceral pain and distension as in the case of patient 1. However, where radical surgery in the form of near-total resection of tumour can be performed with acceptable risks, it might be worthwhile considering in combination with chemotherapy postresection for the minimal residual disease.

When resection is not possible, a variety of other therapeutic modalities have been attempted and these include chemoirradiation, ^{131}I-MIBG, octreotide therapy and arterial embolization.

MIBG scans currently play an important role in diagnosis and follow-up of phaeochromocytomas, specifically its usage in localization of disease where CT scans have failed to detect small tumours. A sensitivity of 77–100% and, more significantly, a specificity of 95–100% have been reported with MIBG scintigraphy.[16] In our case series, it has been invaluable in the detection of sites of recurrence of phaeochromocytomas in patients 3 and 4.

In a therapeutic setting, the intense uptake and prolonged retention of tracer doses of ^{131}I-MIBG by some unresectable phaeochromocytomas formed the basis of attempts to deliver doses large enough to bring about tumour shrinkage.[17] The results are less encouraging, however, with therapeutic activity only in certain highly selected malignant phaeochromocytomas. In their early study of 28 patients, Shapiro and Sisson recorded partial tumour and hormonal responses in only eight cases, with stable disease in 10 and disease progression in the other 10 patients.[18] Five of these 8 cases recurred later with three unresponsive to further MIBG therapy. Since then, therapy with ^{131}I-MIBG has been administered at multiple centres worldwide. A review in 1997 of 116 patients worldwide who had received such treatment revealed less than encouraging numbers overall: 76% symptomatic response, 45% hormonal response and 30% partial tumour regression.[19] There were only five complete responses, all of whom had minimal soft tissue metastases. Rose et al[20] further used 2–3.5 times higher doses of ^{131}I-MIBG in their 12 subjects but yielded only two metastatic cases with complete response, with high rates of haematological toxicity in their patient cohort. Lam et al[21] on the other hand advocate a regimen of multiple intermediate dosage for better tolerance and as a useful adjunct providing longstanding palliation in malignant cases; they were able to demonstrate complete symptomatic and partial tumour volume response in their two patients who have survived 5 and 16 years, respectively. The optimal dose and frequency, as well as tumour and patient selection criteria, remain unknown at this stage.

Due to the resemblance to neuroblastomas, chemotherapy using the CVD regimen can be used. Tumour responses of up to 57% have been reported with minimal side effects, mainly bone marrow toxicity and hypotension. However, most responses are transient without clear effects on long-term survival. This is also reflective of our experience with patients 3 and 4. Presently, there is no evidence available that chemotherapy prolongs patient survival in metastatic disease and should probably be reserved for palliation in symptomatic patients.[10]

Our small case series illustrates the variable clinical outcome of malignant phaeochromocytoma. Patients 1 and 2 demonstrated the more aggressive subtype while patients 3 and 4 may represent the more indolent group. Although noncurative in the metastatic setting, partial tumour resection has contributed to palliation as was seen in patients 1 and 3.

Conclusion

The single most critical element in the management of phaeochromocytoma is probably to consider it in the differential diagnosis when appropriate and to obtain a screening test.[13] Otherwise, surgery in an unprepared patient with an unrecognized phaeochromocytoma can lead to catastrophic cardiovascular complications and mortality.[8]

From the oncological perspective, malignant phaeochromocytoma is extremely rare and the suitable management in metastatic disease remains unknown. The clinical course of metastatic phaeochromocytoma is highly variable and an indolent course can be expected in half of the patients. However, it is impossible to predetermine this, making management and prognostication difficult.

With malignant phaeochromocytoma, there is a place for radical surgery to achieve tumour eradication or symptom palliation provided it can be done with reasonable risks, even in the metastatic setting.

References

1. Stenstrom G, Svardsudd K. Phaeochromocytoma in Sweden 1958–1981. An analysis of the national cancer registry data. *Acta Med Scand* 1986;220:225–32.
2. Bravo EL. Adrenal medullary tumours: pheochromocytomas. In: Mazzaferri EL, Samaan NA, eds. *Endocrine Tumours*. Cambridge: Blackwell Scientific Publications, 1993:Ch 28, 426–47.
3. Remine WH, Chong GC, van Heerden JA, et al. Current management of pheochromocytoma. *Ann Surg* 1974;179:740–8.
4. Karet FE, Brown MJ. Pheochromocytoma: diagnosis and management. *Postgrad Med J* 1994;70:326–8.
5. Ross EJ, Griffith DN. The clinical presentation of phaeochromocytoma. *Q J Med* 1989;71:485–96.
6. Benowitz NL. Pheochromocytoma. *Adv Intern Med* 1990;35: 195–219.
7. Lo CH, Lam KY, Wat MS, et al. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. *Am J Surg* 2000;179: 212–5.
8. St John Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma: review of 50-year autopsy series. *Mayo Clin Proc* 1981;56:354–60.
9. Hartley L, Perry-Keene D. Phaeochromocytoma in Queensland—1970–83. *Aust N Z J Surg* 1985;55:471–5.
10. Averbuch SD, Steakley CS, Young RC, et al. Malignant phaeochromocytoma: effective treatment with a combination of Cyclophosphamide, Vincristine and Dacarbazine. *Ann Intern Med* 1988;109:267–73.

11. Shapiro B, Sisson JC, Lloyd R, et al. Malignant phaeochromocytoma: clinical, biochemical and scintigraphic characterization. *Clin Endocrinol* 1984;20:189.
12. Scharf Y, Nahir AM, Better OS, et al. Prolonged survival in malignant phaeochromocytoma of the organ of Zuckerkandl with pharmacological treatment. *Cancer* 1973;31:746.
13. Orchard T, Grant CS, van Heerden JA, et al. Pheochromocytoma—continuing evolution of surgical therapy. *Surgery* 1993;114: 1153–9.
14. Brennan MF, Keiser HR. Persistent and recurrent pheochromocytoma: the role of surgery. *World J Surg* 1982;6:397–402.
15. Musholt TJ. Surgical management of advanced malignant adrenal tumours. *Eur Surg* 2003;35:97–101.
16. Ilias I, Pacak K. Anatomical and functional imaging of metastatic pheochromocytoma. *Ann N Y Acad Sci* 2004;1018:495–504.
17. Sisson JC, Shapiro B, Beierwaltes WH, et al. Radiopharmaceutical treatment of malignant phaeochromocytoma. *J Nucl Med* 1984;24:197.
18. Shapiro B, Sisson JC. *Atlas of Nuclear Medicine*. Philadelphia: JB Lippincott, 1988:72.
19. Loh KC, Fitzgerald PA, Matthay KK, et al. The treatment of malignant pheochromocytoma with ^{131}I-MIBG: a comprehensive review of 116 reported patients. *J Endocrinol Invest* 1997;20: 648–58.
20. Rose B, Matthay KK, Price D, et al. High-dose ^{131}I-MIBG therapy for 12 patients with malignant pheochromocytoma. *Cancer* 2003; 98:239–48.
21. Lam MG, Lips CJ, Jager PL, et al. Repeated ^{131}I-metaiodobenzylguanidine therapy in two patients with malignant pheochromocytoma. *J Clin Endocrinol Metab* 2005;90:5888–95.